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Contemporary Management of Acute Ischemic Stroke

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Keywords

acute stroke treatment, acute ischemic stroke, thrombolysis, thrombectomy, endovascular treatment, antithrombotic treatment

Abstract

In the past decade, adding mechanical thrombectomy (MT) of intracranial arterial occlusions to intravenous (IV) thrombolysis has revolutionized the treatment of acute ischemic stroke (AIS) by expanding the therapeutic window to 24 h. Treatment decisions require establishing a high probability of AIS; confirming time since last known well (LKW); assessing severity of the neurological deficit; determining any contraindications to IV thrombolysis; and performing neuroimaging, usually noncontrast computed tomography (NCCT), to exclude intracerebral hemorrhage. If time since LKW is less than 4.5 h, patients with disabling stroke without contraindications can proceed immediately to IV thrombolysis while the decision about MT is under way. For some patients, the MT decision can be made on the basis of clinical assessment, NCCT, and CT angiography showing a large vessel occlusion. Others may require additional neuroimaging. Patients who are not candidates for IV thrombolysis within 4.5 h or MT should be immediately evaluated for eligibility for extended-window IV thrombolysis or early antiplatelet treatment.

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INTRODUCTION

Since 2015, data from randomized controlled trials (RCTs) of mechanical thrombectomy (MT) have expanded the treatment of acute ischemic stroke (AIS) in selected patients from the 4.5-h window for intravenous (IV) thrombolytic drugs to 24 h. More recently, studies have shown that dual antiplatelet treatment reduces early recurrence for patients with minor strokes who are ineligible for IV thrombolysis or MT. This article reviews the current management of arterial AIS in adults based on evidence from these trials. For management of AIS due to cerebral venous thrombosis or for pediatric stroke, we refer the reader elsewhere (1, 2).

APPROACH TO PATIENTS WITH SUSPECTED ACUTE ISCHEMIC STROKE

The rapid onset of focal neurological deficits restricted to a single cerebral arterial territory is the archetypal clinical presentation for AIS. However, distinction between AIS and intracerebral hemorrhage (ICH) on clinical grounds is not reliable; brain imaging is necessary (3). Noncontrast computed tomography (NCCT) is the preferred modality to identify ICH because of its rapidity, availability, and sensitivity. Magnetic resonance imaging (MRI) can be used, but it takes longer (4). MRI with diffusion-weighted imaging (MRI-DWI) is more sensitive than NCCT for detecting AIS (5). Nevertheless, for many patients with typical presentations, NCCT showing no other explanation for the neurological deficit is sufficient initial imaging to diagnose and treat AIS.

Because the benefits of treatments are time sensitive, the initial assessment of the patient with suspected AIS should be performed quickly. Treatment options depend on time from stroke onset, severity of neurological deficit, and neuroimaging. Time from onset is measured from when patients can be confirmed to have been in their baseline state, often termed last known well (LKW). For patients who awaken with stroke, LKW will be some time before or when they went to sleep. The National Institutes of Health Stroke Scale (NIHSS) is commonly used to measure the severity of neurological deficit. The scale ranges from 0 to 42, where lower numbers indicate milder deficits (6). The severity of neurological deficit is further characterized as nondisabling or as disabling if it would prevent the performance of basic activities of daily living or returning to work.

In addition to excluding ICH, NCCT is used to determine the Alberta Stroke Program Early Computed Tomography Score (ASPECTS). This 0-to-10 score is based on ischemic changes in the middle cerebral artery (MCA) territory, with 0 being the worst (7). Additional neuroimaging beyond NCCT may be required to determine eligibility for some interventions. Contrast CT angiography (CTA) or MR angiography (MRA) is used to demonstrate the location of arterial occlusions. CT perfusion (CTP) and MRI-DWI are used to estimate the area of ischemic brain tissue that is likely irreversibly damaged (i.e., the core). Delayed contrast arrival on CTP or MRI perfusion (MRP) is used to estimate the area of ischemic tissue that is potentially salvageable by reestablishing blood flow (i.e., the penumbra) (8, 9).

The effects of treatments are most commonly assessed using the modified Rankin Scale (mRS) for functional disability. Scores range from 0 (no symptoms) to 6 (death). mRS 1 indicates an ability to carry out all usual activities despite symptoms. mRS 2 indicates an ability to look after one's affairs without assistance but an inability to carry out all previous activities. mRS 3 indicates a requirement for some help to manage one's affairs but an ability to walk unassisted (10).

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INTRAVENOUS THROMBOLYSIS WITH RECOMBINANT TISSUE PLASMINOGEN ACTIVATORS

Early Alteplase Within 4.5 Hours of Last Known Well

IV alteplase (0.9 mg/kg, maximum dose 90 mg, over 60 min with the initial 10% of the dose given as a bolus over 1 min) given within 4.5 h of LKW reduces disability from AIS in patients who meet stringent eligibility criteria (4, 11). IV alteplase benefits patients with disabling stroke regardless of NIHSS. IV alteplase is not recommended for patients with nondisabling stroke with NIHSS 0–5 because it is not superior to antiplatelet treatment (12, 13).

The benefit of IV alteplase is time dependent. The adjusted odds ratios (aORs) of mRS 0–1 at 3 months are 2.55 (95% CI, 1.44–4.52; 41.6% versus 29.1%) for treatment within 0–90 min of LKW, 1.64 (95% CI, 1.12–2.40; 41.9% versus 28.9%) for 91–180 min, and 1.34 (95% CI, 1.06–1.68; 45.0% versus 38.2%) for 181–270 min (11).

Symptomatic ICH occurs in 3.4% of patients treated with IV alteplase within 4.5 h versus 0.5% in controls (14). Symptomatic ICH is more common in those with more severe strokes, but even when the increased risk is taken into account, the overall benefit of IV alteplase on functional outcome is still present, irrespective of disabling stroke severity (15).

Prior to the administration of IV alteplase, brain imaging is required to exclude ICH. Further imaging beyond NCCT is rarely necessary. While normal MRI-DWI may help exclude certain conditions that can mimic AIS, such as migraine, seizures, and peripheral vestibulopathy, the hemorrhage risk in such patients is so low that the delay in obtaining MRI-DWI is rarely justified (16). Blood glucose should be measured rapidly to exclude hypoglycemia mimicking stroke (4, 17). RCTs demonstrating a benefit of early IV alteplase encompassed long lists of ineligibility criteria designed to exclude patients with minimal deficits, increased risk of bleeding, and stroke mimics. Many of these criteria have been carried over to current guidelines as contraindications, even though they have not always been shown to identify patients who do not benefit (4). Given the low prevalence of unsuspected coagulation abnormalities in patients without history or suspicion of a coagulopathy, IV thrombolytic administration can commence while the results of hematological testing are pending (18). Unless special tests show no anticoagulant effect, IV thrombolysis is not recommended for patients who have used direct-acting anticoagulants within the previous 48 h on the basis of opinion that bleeding risk would be excessive, although several recent observational studies have suggested that this may not be the case (4, 17, 19–21). There has been a single case report of fatal ICH following IV tissue plasminogen activator (tPA) in a patient with AIS who was receiving lecanemab, a recently US Food and Drug Administration (FDA)–approved monoclonal antibody directed against beta-amyloid for the treatment of early Alzheimer disease that can cause hemorrhagic vasculopathy (22). Caution has been urged in administering tPA to patients with AIS receiving this and similar monoclonal antibodies, but current data are inadequate to provide definitive evidence-based guidelines based on comprehensive risk–benefit assessments (23). Fortunately, many patients with contraindications to IV thrombolysis are eligible for MT.

According to the original tPA trial protocol (24), blood pressure is kept below 185/110 mm Hg before and during infusion and below 180/105 mm Hg for at least the first 24 h afterward. Treatment to a lower systolic blood pressure of 130–140 mm Hg does not reduce the risk of ICH or improve outcome (25).

Alteplase for Strokes More Than 4.5 Hours from Last Known Well

IV alteplase more than 4.5 h after LKW is beneficial for patients selected by additional imaging beyond NCCT: MRI for those with wake-up strokes who can be treated within 4.5 h of awakening

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or perfusion imaging for those up to 9 h from LKW (26, 27). The same contraindications for earlier alteplase apply.

Tenecteplase

Tenecteplase is a recombinant tPA with a longer plasma half-life than alteplase. It is given as an IV bolus rather than as a 1-h infusion. Several large RCTs have shown the noninferiority of an IV tenecteplase 0.25 mg/kg bolus (maximum 25 mg) compared to IV alteplase in patients within 4.5 h of LKW for both functional outcome and risk of symptomatic ICH (28, 29). Recent Canadian and European stroke treatment guidelines specify tenecteplase as an alternative to alteplase within 4.5 h of LKW (17, 30).

Intravenous Thrombolysis Bridging to Mechanical Thrombectomy

Patients with AIS may be eligible for both IV thrombolysis and MT (see the next section). Many RCTs demonstrating a benefit of MT included patients who also received IV thrombolysis. Noninferiority of MT alone in comparison to IV thrombolysis plus MT cannot be demonstrated (30). Therefore, combined use is recommended for patients eligible for both (17, 31, 32). Either alteplase or tenecteplase can be used.

MECHANICAL THROMBECTOMY

MT utilizes endovascular techniques employing stent retrievers or direct aspiration catheters to mechanically remove occluding thrombi in the larger intracranial arteries [i.e., large vessel occlusion (LVO)] (**Figure 1**).

0–6 Hours from Last Known Well

Published in 2015, the MR CLEAN RCT demonstrated a significant benefit of MT within 6 h of LKW for reducing 90-day disability in comparison to patients receiving standard medical care alone, including IV tPA (mRS 0–2, 32.6% versus 19.1%; aOR, 2.16; 95% CI, 1.39–3.38) (34). Given these data, four similar RCTs that were ongoing at the time underwent interim analyses that demonstrated comparable results (35). Inclusion and exclusion criteria for these trials were similar but not identical. Most patients were 18 years or older, had prestroke mRS 0–1, had NIHSS $\geq$6, could be treated within 6 h from LKW, had ASPECTS $\geq$6, and had a causative LVO of the intracranial internal carotid artery (ICA) or of the M1 or M2 segment of the MCA (35). As a result, guidelines from the American Heart Association and the American Stroke Association strongly recommend treatment of such patients with MT, with less strong recommendations for patients with different ASPECTS, NIHSS, premorbid mRS, or occlusion sites (4). Neuroimaging beyond NCCT and CTA/MRA was used to determine eligibility in most of these trials, albeit different in each. However, since two RCTs with eligibility criteria based only on NCCT and CTA/MRA showed benefit, current guidelines do not recommend any imaging beyond NCCT and CTA/MRA for treatment decisions (4, 17). A time-dependent effect is observed with MT within 0–6 h, with a decline in the odds of better functional outcomes (better mRS at 90 days) at 3 h from LKW [common odds ratio (cOR), 2.79; 95% CI, 1.96–3.98] versus 6 h (cOR, 1.98; 95% CI, 1.3–3.0) (36).

6–24 Hours from Last Known Well for Anterior Circulation Large Vessel Occlusion

In 2018, two RCTs expanded the time window for MT, using specific imaging markers to select patients (8, 9). DAWN included patients within 6–24 h of LKW, prestroke mRS 0–1, and causative

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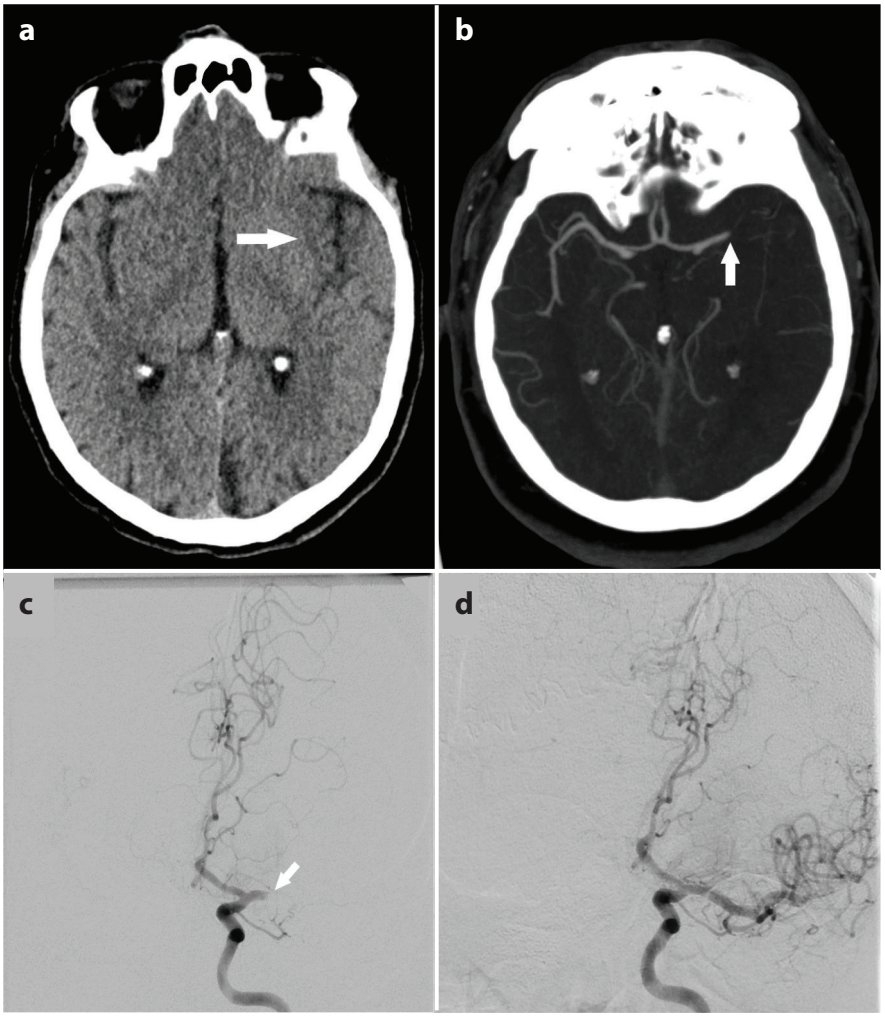

Figure 1

(*a*) Noncontrast computed tomogram of the head (transverse section) showing slight hypodensity in the left insular cortex (*white arrow*). (*b*) Computed tomography angiogram (transverse section) showing occlusion of the stem of the left middle cerebral artery (*white arrow*). (*c*) Cerebral arteriogram (anterior projection) showing occlusion of the stem of the left middle cerebral artery prior to mechanical thrombectomy (*white arrow*). (*d*) Cerebral arteriogram (anterior projection) showing recanalization of the stem of the left middle cerebral artery. Figure reproduced with permission from Reference 33; copyright 2020 Massachusetts Medical Society.

LVO of the intracranial ICA or M1. Either CTP or MRI-DWI was used to determine the core. Patients were included when the neurological deficit was considered too large for the core (thus indicating a substantial penumbra) based on one of three different categories determined by age, NIHSS, and core volume. Those receiving MT had a significantly higher chance of functional independence (mRS 0–2) at 90 days (49% versus 13%; adjusted difference, 33%; 95% CI, 21%–44%) (8). The DEFUSE 3 trial included patients within 6–16 h of LKW, prestroke mRS 0–2, and causative LVO of the intracranial ICA or M1. Either CTP or MRP-DWI was used to determine the core and penumbra. Patients were included if they met specifications for a large area

of penumbra without a large core. Patients receiving MT had significantly reduced disability at 90 days (aOR, 3.36; 95% CI, 1.96–5.77; $p < 0.001$; mRS 0–2, 45% versus 17%) (9). Most of the participants in both trials also had ASPECTS ≥6.

On the basis of these trials, patients presenting within 6–16 h of LKW should be treated with MT if they fulfill the eligibility criteria of either the DEFUSE 3 or DAWN clinical trial. For patients presenting within 16–24 h of LKW, treatment with MT is recommended if they fulfill the DAWN eligibility criteria (4).

These initial anterior circulation LVO MT trials excluded patients with a presumed large volume of irreversible ischemic damage on the basis of either ASPECTS or infarct core as observed on CTP or MRI-DWI. In 2023, two large RCTs, ANGEL–ASPECT and SELECT2, enrolled patients who would generally otherwise be candidates for anterior circulation LVO MT within 24 h but had a large core by brain imaging, determined primarily by ASPECTS 3–5. Although the benefit was not as robust as in patients with less radiographically extensive brain damage, both trials demonstrated a significant shift toward improved functional outcomes (better mRS) at 90 days with MT (ANGEL–ASPECTS: OR, 1.37; 95% CI, 1.11–1.69; $p = 0.004$; mRS 0–2; 30.0% versus 11.6%; SELECT2: OR, 1.51; 95% CI, 1.20–1.89; $p < 0.001$; mRS 0–2; 20.3% versus 7%) (37, 38). Subsequent publication of two similar RCTs (TENSION and LASTE) reported comparable results (39, 40). MT should be considered in patients within 24 h of LKW who have causative LVO of the intracranial ICA or M1 and already have a presumed large infarct core as seen on imaging (ASPECTS 3–5), although most such patients will still be left disabled.

Basilar Artery Occlusion

Two RCTs published in 2022, ATTENTION and BAOCHE, demonstrated higher rates of independent ambulation or better (mRS 0–3) at 90 days in patients receiving MT for basilar artery occlusions (ATTENTION: adjusted rate ratio, 2.06; 95% CI, 1.46–2.91; $p < 0.001$; mRS 0–3; 46% versus 23%; BAOCHE: adjusted rate ratio, 1.81; 95% CI, 1.26–2.60; $p < 0.001$; mRS 0–3; 46% versus 24%). ATTENTION included patients with LKW 0–12 h, while BAOCHE included patients with LKW 6–24 h (41, 42). Both used the posterior circulation version of ASPECTS (PC-ASPECTS) to characterize the degree of ischemic damage and determine eligibility. Similar to ASPECTS, a lower score indicated a larger degree of ischemia, and both trials excluded patients with PC-ASPECTS <6 (43).

Blood Pressure After Mechanical Thrombectomy

Most RCTs of MT used the postprocedure blood pressure protocol of below 180/110 mm Hg from the IV thrombolysis trials. Recently, RCTs have demonstrated worse functional outcomes with more intensive blood pressure control to a systolic blood pressure below 140 mm Hg (44, 45). Currently, a reasonable goal following successful MT is a systolic blood pressure of 140–180 mm Hg, which is also suitable for the many patients receiving MT who have also received IV tPA.

ANTITHROMBOTIC AGENTS

For patients treated with IV thrombolysis, anticoagulant or antiplatelet administration is generally delayed for 24 h to minimize bleeding risk (4).

Antiplatelet Agents

Pooled data from two large RCTs showed that aspirin 160–300 mg administered within 48 h after AIS decreased the incidence of further stroke or death in the hospital (8.2% versus 9.1%;

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$p = 0.001$) versus a placebo (46). In the absence of contraindications or other superseding therapy that has proven superior, all patients with AIS should receive early aspirin.

RCTs evaluating early dual-antiplatelet treatment (DAPT) in comparison to aspirin have been limited to patients with minor strokes and no indication for long-term anticoagulation. These studies have varied somewhat in design, using eligibility criteria of either NIHSS ≤ 3 or ≤ 5, time windows of 12–72 h, different DAPT regimens (clopidogrel plus aspirin or ticagrelor plus aspirin), treatment durations of 21–90 days, and other variations. All of these RCTs excluded patients who received IV thrombolysis or had planned MT (47–50). In aggregate, these trials show an absolute risk reduction in recurrent ischemic stroke by DAPT initiated within the first 72 h of 2.7% (OR, 0.73; 95% CI, 0.65–0.82) with a concomitant absolute increase in the risk of clinically important bleeding of 0.35% (OR, 2.36; 95% CI, 1.19–4.69). The reduction in recurrent stroke is observed primarily within the first week, and the increased bleeding risk endures for the duration of DAPT. While the benefits of a short course of early DAPT in patients after mild stroke are clear, consensus has not yet emerged on the optimal eligibility criteria and duration of therapy.

Anticoagulants

A meta-analysis of more than 20,000 patients from eight RCTs showed that full-dose therapeutic anticoagulation with heparin or similar drugs started within 48 h of AIS and continued for 10 to 14 days does not reduce the rate of death or disability at 3–6 months in comparison to aspirin or a placebo (OR, 0.99; 95% CI, 0.9–1.04; 59.4% versus 59.9%) (51). Similar neutral outcomes occurred in the subgroup with atrial fibrillation (OR, 0.97; 95% CI, 0.79–1.20; 78.1% versus 78.5%) (52). Additional analyses did not identify any subgroup with benefit or harm, including those with severe strokes (53). On the basis of these data, early full anticoagulation with heparin or similar drugs is rarely indicated for the treatment of AIS, even in patients with associated atrial fibrillation. It is occasionally employed in unusual circumstances, such as when AIS is associated with intracardiac chamber thrombi, nonbacterial thrombotic endocarditis, or intraluminal carotid artery thrombi, based on anecdote, small observational studies, and mechanistic assumptions.

When started an average of 14 days after AIS in patients with atrial fibrillation detected by electrocardiogram, oral anticoagulation with vitamin K antagonists is superior to aspirin for long-term prevention of recurrent ischemic stroke, reducing the risk from 10% per year to 4% per year (hazard ratio, 0.38; 95% CI, 0.23–0.64) with only a 2% increase in major bleeding (54). For long-term stroke prevention in patients with atrial fibrillation, direct-acting anticoagulants are preferred to warfarin (except for those with mitral stenosis or mechanical valves) due to comparable efficacy in preventing stroke or systemic embolism and lower bleeding risk (55, 56). In patients with atrial fibrillation with recent AIS, the risk of symptomatic ICH from starting direct-acting oral anticoagulants within 2 weeks at 0–0.5% is lower than with heparin and does not differ for early initiation within 4 days versus later (57, 58). Optimal timing for initiation is the subject of active investigation.

BLOOD PRESSURE MANAGEMENT

In hypertensive patients with blood pressures lower than 220/120 mm Hg who did not receive IV thrombolytics or undergo MT and who have no coexisting medical conditions that require urgent antihypertensive treatment, multiple RCTs have shown that starting or continuing antihypertensive medications within the first 48–72 h after the onset of AIS does not alter the risk of death or disability (4, 17). No comparable RCT data exist for those with blood pressures of 220/120 mm Hg or higher. Cerebral blood flow measurements in chronically hypertensive people suggest that rapid reductions in blood pressure of up to 15% are usually safe, but they remain of unknown value (59).

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If this approach is undertaken, close monitoring of neurological status is advisable to stop treatment if worsening occurs (4). These data apply only to the very early management of hypertension. Long-term blood pressure control is a cornerstone of secondary stroke prevention (60).

MANAGEMENT OF BRAIN SWELLING

During the first few days, patients with large cerebral or cerebellar infarctions are at a high risk for fatal brain swelling. Medical measures to reduce intracranial pressure, such as mannitol or hypertonic saline, are often ineffective, whereas surgical decompressive craniectomy and durotomy can be lifesaving. However, those with large cerebral infarctions who survive may be left with significant disability, especially if older than 60 years. This possibility should be considered when discussing treatment options (61).

GENERAL AND SUPPORTIVE CARE

In-hospital care by specialized teams improves outcomes for patients with AIS. Improvement is most evident when care is provided in a geographically defined stroke unit. Whenever possible, all patients with AIS should be admitted to such units. For additional specific recommendations on supportive care, see the guidelines published elsewhere (4, 17).

SYSTEMS OF CARE

The benefits of IV thrombolysis and early MT are time dependent, necessitating a dramatic shift in systems of care to rapidly triage, diagnose, and treat patients. Many institutions have instituted "CODE STROKE" pathways that emphasize immediate clinical evaluation and emergent NCCT with the goal of delivering IV thrombolysis within 30 min and then rapidly assessing the patient's eligibility for MT, which requires at least additional CTA or MRA and perhaps MRI-DWI or perfusion imaging.

The past decade has also witnessed major organizational changes in regional systems of stroke care to account for the varying capabilities of individual institutions, particularly the development of hub-and-spoke models centered around comprehensive stroke centers providing MT. Hospitals that assess patients and administer IV thrombolysis but lack other capabilities may routinely transfer patients for subsequent care ("drip-and-ship") or for consideration of MT. Other hospitals may be able to manage patients after routine IV thrombolysis but need to work closely with stroke centers to rapidly evaluate and transfer patients who are eligible for MT or may require more specialized care, such as decompressive craniectomy. Evaluation by telemedicine (i.e., telestroke) can be key for rapid evaluation and triage. Even institutions that do provide MT may, at times, still find it prudent to transfer more complex patients to comprehensive stroke centers with a wider variety and immediate availability of experts. Within each geographical area, neurological assessment by emergency medical services personnel, service response times, and ambulance travel times will inform decisions about the hospital to which patients should be initially transported. These networks need to be developed and maintained in order to be able function efficiently when needed (62).

Mobile stroke units (MSUs) are ambulances equipped with a CT scanner, point-of-care laboratory testing, a dedicated telemedicine link to a stroke center, and specially trained personnel. Patients with suspected stroke receive their initial clinical evaluation, CT imaging, and IV thrombolysis decision at the point of pickup. MSUs reduce onset-to-treatment time, increase the percentage of patients who get IV thrombolytics within 1 h, and improve functional outcomes. These benefits have accrued in urban and suburban settings as part of already highly organized systems of stroke care (63). MSUs are expensive, with annual costs approximating US$1 million

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(64). While clearly effective in certain circumstances, their place in the overall system of modern stroke care will take some time to determine.

SUMMARY OF CURRENT MANAGEMENT

Two immediate decisions must be made for patients with suspected AIS: Are they a candidate for IV thrombolysis, and are they a candidate for MT? These decisions require careful clinical evaluation to establish the high probability of AIS, confirm LKW, assess the severity of the neurological deficit, and determine whether there are any contraindications to IV thrombolysis. Neuroimaging, usually NCCT, is required to exclude ICH. If hypoglycemia is excluded and LKW <4.5 h, those with disabling stroke without contraindications can proceed immediately to IV thrombolysis while the decision for MT eligibility is underway. The MT decision will, at a minimum, require angiography to assess for LVO, usually CTA, which is often acquired at the time of NCCT. For some patients, the decision regarding MT can be made on the basis of clinical assessment, NCCT, and CTA. Such patients include those with disabling stroke who have intracranial anterior circulation LVO (ICA, M1, or M2), LKW <6 h, and ASPECTS ≥3 as well as those with disabling basilar artery occlusion, LKW <24 h, and PC-ASPECTS ≥6. For those who have disabling anterior circulation LVO and are within 6–24 h of LKW, the decision about MT is not so straightforward. DAWN and DEFUSE 3 enrolled patients mostly with ASPECTS ≥6 from 6 to 24 h and 6 to 16 h, respectively, but also used further eligibility criteria based on CTP and MRI. Neither trial was based on data demonstrating that such additional eligibility criteria were necessary. ANGEL–ASPECT, SELECT2, TENSION, and LASTE, all of which predominantly enrolled patients with ASPECTS 3–5, did not require additional perfusion imaging and showed a benefit of MT within 24 h for these patients with more severe strokes. Data from these four trials have raised questions about the need for additional imaging criteria, such as those used in DAWN and DEFUSE 3, for patients with ASPECTS ≥6 in the 6–24-h window. Large observational studies have shown equivalent outcomes in patients who were selected by ASPECTS ≥6 and CTA only in comparison to those selected on the basis of additional DAWN or DEFUSE 3 imaging criteria (65). While a large RCT of patients with ASPECTS ≥6 in the 6–24-h window would be necessary to definitively settle this issue, data from the existing RCTs and observational studies may be enough to shift practice.

Patients who are not candidates for IV thrombolysis given within 4.5 h or MT should be immediately considered for neuroimaging to determine eligibility for extended-window IV thrombolysis, if they qualify clinically. For patients who are ineligible for any IV thrombolysis or MT, DAPT should be initiated for those eligible with minor stroke and aspirin alone for those with more severe deficits.

FUTURE DIRECTIONS

Logistical barriers to providing time-sensitive therapies remain. While further expansion of telestroke with the drip-and-ship paradigm should lead to greater availability of IV thrombolysis, local travel times in rural areas will still impose barriers to rapid treatment, especially timely access to MT performed by qualified neurointerventionalists in centers with comprehensive periprocedural care teams. Not every hospital can provide such services, since a sufficient number of cases is required to economically support the necessary personnel and infrastructure. This situation would best be solved by cooperation among regional healthcare systems, not by competition for market share.

Even with the clear benefits of IV thrombolysis and MT in eligible patients, a substantial portion of these patients do not return to their baseline. Consequently, research efforts are being

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devoted to both improving existing therapies and adding adjunct therapies. Targets for improved thrombolytics include agents with increased clot specificity and/or reduced hemorrhage risk. Adjunct therapies may take the form of neuroprotective agents administered before or after treatment. The addition of antithrombotic medications to both IV thrombolysis and MT (including intra-arterial thrombolytics after MT) in an attempt to improve initial reperfusion or prevent subsequent reocclusion is under active investigation.

While many patients who do not meet IV thrombolysis criteria can be treated with MT, there remains a group without LVO who arrive too late. Attempts to use CTP and/or MRI to identify a subset of these patients who still could benefit from IV thrombolysis have so far been unsuccessful. Furthermore, data are limited for patients with an LVO and more than 24 h from LKW, and the efficacy of MT in these patients has not yet been demonstrated.

Data on the efficacy of MT for patients with milder strokes (NIHSS <6) and/or distal occlusions (anterior cerebral artery, M3 segment of the MCA, posterior cerebral artery) are limited. Since many patients with these milder deficits can achieve good outcomes without treatment, RCTs with endpoints sensitive to milder degrees of impairment will be necessary.

On the basis of the eligibility criteria in the relevant RCTs, the use of short-term DAPT started within a few days is restricted to patients with mild strokes because of the fear of intracranial bleeding. This fear is likely unfounded. Future RCTs should expand eligibility to include patients with more severe deficits.

DISCLOSURE STATEMENT

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